THE FOLLOWING ARE THE ENGLISH TRANSLATION
OF ANNEXES TO THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT (ARTICLE 34):

Amended Sheets (Pages 38-46)

## CLAIMS

1.    The use, as a specific marker for the beta cells of pancreatic islets of Langerhans, of at least one isolated polynucleotide or of the corresponding protein, chosen from:

- the polynucleotides comprising or having one of the following sequences: (a) the sequence SEQ ID NO. 1, (b) a fragment of the sequence SEQ ID NO. 1 of at least 15 consecutive nucleotides, (c) a sequence exhibiting a percentage identity of at least 80%, after optimal alignment, with one of the sequences defined in (a) or in (b), and (d) a sense or antisense sequence complementary to one of the sequences defined in (a), (b) or (c), and

- the proteins encoded by the polynucleotides as defined in (a), (b), (c) or (d) above, comprising or having one of the following sequences: (e) the sequence SEQ ID NO. 2, (f) a fragment of the sequence SEQ ID NO. 2 of at least 15 consecutive amino acids, (g) a sequence exhibiting a percentage identity of at least 60%, after optimal alignment, with one of the sequences defined in (e) or in (f) or at least 65% similarity, preferably 80% identity or at least 90% similarity, or even more preferably 90% identity or at least 95% similarity.

2.    The use as claimed in claim 1, characterized in that said isolated polynucleotide as defined in (c) is a polynucleotide that is a variant of the sequence SEQ ID NO. 1, comprising a mutation which results in a modification of the amino acid sequence of the protein encoded by the sequence SEQ ID NO. 1.

3.    The use as claimed in claim 1, characterized in that said isolated polynucleotide as defined in (b) or in (d) is chosen from the pair of primers SEQ ID NO. 3 and SEQ ID NO. 4 and the pair of primers SEQ ID NO. 5 and SEQ ID NO. 6.

4.    The use as claimed in claim 1,

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characterized in that said isolated polynucleotide can be obtained by amplification using the pair of primers as defined in claim 3.

5.    The use as claimed in claim 1, characterized in that said polynucleotide as defined in (d) is a small interfering RNA (siRNA) which, by interaction with the mRNAs corresponding to said polynucleotide, will bring about their degradation.

6.    The use as claimed in claim 1, characterized in that said protein as defined in (g) is a variant of the sequence SEQ ID NO. 2, that has a mutation associated with diabetes or with hyperinsulinism.

7.    The use as claimed in claim 1, characterized in that said fragment as defined in (f) has a sequence chosen from the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10.

8.    An isolated polynucleotide that can be used as claimed in claim 1, characterized in that it comprises or has a sequence chosen from:

(a)    the sequence SEQ ID NO. 1,

(b)    a fragment of the sequence SEQ ID NO. 1 of at least 20 consecutive nucleotides,

(c)    a sense or antisense sequence that is complementary to one of the sequences defined in (a), (b) or (c),

with the exception of the fragments of at least 15 consecutive nucleotides included in the sequences having the accession numbers, in the NCBI database, No. AX526723, No. AX526725 and No. AX526727, of the ESTs having the accession numbers, in the GenBank database, BM565129, BM310003, BM875526, BG655918, BQ417284, BQ267316, BU072134, BQ267526, BQ270198, BU581447, BU070173, BQ631692 and BU949895, and also of the sequences having the accession numbers, in the NCBI database, AX526723, AX526725 and AX526727.

9.    A probe for detecting, identifying or

assaying nucleic acids corresponding to the polynucleotides as defined in claim 1, characterized in that it consists of a polynucleotide as claimed in claim 8.

5        10. A pair of primers for amplifying nucleic acids that can be used as claimed in claim 1, characterized in that it is chosen from the pairs of primers as defined in claim 3.

         11. An isolated polynucleotide that can be
10  used as claimed in claim 1, that can be obtained by amplification using the primers as claimed in claim 10.

         12. The polynucleotide as claimed in claim 8 or claim 11, characterized in that it is a small interfering RNA corresponding to the polynucleotide as
15  defined in claim 1, which, by interaction with the mRNAs corresponding to said polynucleotide, will bring about their degradation.

         13. A method for determining the transcription profile of the gene corresponding to the
20  polynucleotide as claimed in claim 8 or claim 11,  or an alteration of said profile, in a biological sample, comprising a first step consisting in obtaining, by any appropriate means, the RNAs from the biological sample, a second step consisting in bringing said RNAs into
25  contact with a labeled probe consisting of a polynucleotide as claimed in any one of claims 8, 9 or 11, under conditions appropriate for hybridization between the RNAs and the probe, and a third step consisting in revealing, by any appropriate means, the
30  hybrids formed.

         14. The method as claimed in claim 13, in which the second step is a step consisting of reverse transcription and/or of amplification of the transcripts, carried out using a pair of primers as
35  claimed in claim 10, and the third step is a step consisting in revealing, by any appropriate means, the amplified nucleic acids.

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15. The method as claimed in either one of claims 13 or 14, characterized in that it also comprises a step consisting in evaluating the level of transcription of the gene by comparison with a control

5    selected beforehand.

16. A method for demonstrating the gene corresponding to the polynucleotide as claimed in claim 8 or claim 11 or the allelic variants of said gene or a functional alteration of this gene, in a

10   biological sample, comprising a first step consisting in obtaining, by any appropriate means, the DNA from the biological sample, a second step consisting in bringing said DNAs into contact with a labeled probe consisting of a polynucleotide as claimed in any one of

15   claims 8, 9 or 11, under conditions appropriate for hybridization between the DNAs and the probe, and a third step consisting in revealing, by any appropriate means, the hybrids formed.

17. The method as claimed in claim 16, in

20   which the second step is an amplification step carried out using a pair of primers as claimed in claim 10 and the third step is a step consisting in revealing, by any appropriate means, the amplified nucleic acids formed.

25   18. The method as claimed in either one of claims 16 or 17, characterized in that it also comprises a step consisting in isolating and sequencing the nucleic acids demonstrated.

19. A kit of reagents for carrying out the

30   methods as claimed in any one of claims 13 to 18, comprising:

a)    at least one probe as claimed in claim 9 and/or one pair of primers as claimed in claim 10;

b)    the reagents required for carrying out a

35   hybridization reaction between said probe and/or said primers and the nucleic acid of the biological sample;

c)    the reagents required for carrying out

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an amplification reaction;

     d)   the reagents required for detecting and/or assaying the hybrid formed between said probe and the nucleic acid of the biological sample, or the amplified nucleic acids formed.

     20. A DNA chip comprising at least one polynucleotide as claimed in claim 8 or claim 11.

     21. The use of a polynucleotide as claimed in claim 8 or claim 11, for preparing a DNA chip.

     22. The use, *in vitro*, of the polynucleotide as claimed in any one of claims 8, 11 or 12, as a means for studying:

     a)   the overexpression of the transporter encoded by the polynucleotide as claimed in claim 8 or claim 11 in model cell lines and the impact on insulin secretion in response to a stimulation with glucose;

     b)   the sensitivity of the cells to cell death (apoptosis) induced by conditions of oxidative stress or of low or high zinc concentration;

     c)   the steps of differentiation of stem cells into insulin-secreting cells in response to various exogenous stimulations.

     23. A cloning and/or expression vector, characterized in that it comprises an insert consisting of a polynucleotide as claimed in any one of claims 8, 11 or 12.

     24. A cell modified with a polynucleotide as claimed in any one of claims 8, 11 or 12 or a vector as claimed in claim 23.

     25. A non-human transgenic organism, characterized in that all or some of its cells contain a polynucleotide as claimed in any one of claims 8, 11 or 12 or a vector as claimed in claim 23, in a free or integrated form.

     26. The use of a modified cell as claimed in claim 24 or of a non-human transgenic organism as claimed in claim 25, for producing a protein or a

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protein fragment encoded by a polynucleotide as claimed
in claim 8 or claim 11, or chosen from the sequences
SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID
NO. 10.

5          27.  A method for preparing a protein or a
protein fragment encoded by a polynucleotide as claimed
in claim 8 or 11, or chosen from the sequences SEQ ID
NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10,
characterized in that it comprises culturing modified
10   cells as claimed in claim 24, in particular mammalian
cells, or cells from non-human transgenic organisms as
defined in claim 25, under conditions that allow the
expression of said protein, and purifying said
recombinant protein.

15          28.  The use of a monoclonal or polyclonal
antibody specific for the protein of SEQ ID NO. 2, for
detecting and/or sorting islets of Langerhans or else
beta cells.

          29.  The use of a monoclonal or polyclonal
20   antibody specific for the protein of SEQ ID NO. 2, for
analyzing the differentiation of stem cells into
pancreatic islet cells, preferably into beta cells.

          30.  A method for selecting the beta cells of
islets of Langerhans, comprising a first step
25   consisting in bringing the cells of a biological sample
liable to contain such islets and/or cells into contact
with a monoclonal or polyclonal antibody specific for
the protein of SEQ ID NO. 2, a second step consisting
in demonstrating, by any appropriate means, the cells
30   labeled with the antibody, and a third step consisting
in isolating, by any appropriate means, the labeled
cells.

          31.  A method for analyzing the
differentiation of stem cells into pancreatic islet
35   cells or into beta cells, comprising a step consisting
in bringing the cells of a biological sample liable to
contain said stem cells undergoing differentiation into

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contact with a monoclonal or polyclonal antibody specific for the protein of SEQ ID NO. 2, a second step consisting in demonstrating, by any appropriate means, the cells labeled with the antibody, and a third step
5    consisting in visualizing, by any appropriate means, the labeled cells.

        32. The method as claimed in claim 31, also comprising an additional step consisting in isolating, by any appropriate means, the labeled cells.

10       33. A method of screening for a chemical or biochemical compound that can directly or indirectly interact, *in vitro* or *in vivo*, with the polynucleotide as claimed in either one of claims 8 or 11, characterized in that it comprises a first step
15   consisting in bringing a candidate chemical or biochemical compound into contact with the polynucleotide as claimed in either one of claims 8 or 11 or a cell as claimed in claim 24 or a non-human transgenic organism as claimed in claim 25 or a DNA
20   chip as claimed in claim 20, and a second step consisting in detecting the complex formed between the candidate chemical or biochemical compound and the polynucleotide or the cell or the non-human transgenic organism or the DNA chip.

25       34. A method of screening for a chemical or biochemical compound that can directly or indirectly modulate, *in vitro* or *in vivo*, the expression of the polynucleotide as claimed in either one of claims 8 or 11, characterized in that it comprises a first step
30   consisting in bringing a candidate chemical or biochemical compound into contact with a polynucleotide as claimed in either one of claims 8 or 11 or a cell as claimed in claim 24 or a non-human transgenic organism as claimed in claim 25 or a DNA chip as claimed in
35   claim 20, and a second step consisting in measuring, by any appropriate means, the expression of the polynucleotide as claimed in either one of claims 8 or

11.

     35. A method of screening for a chemical or biochemical compound that can potentially be used for the treatment of diabetes and of hyperinsulinism, characterized in that it comprises a first step consisting in bringing a candidate chemical or biochemical compound into contact with a protein or a protein fragment encoded by a polynucleotide as claimed in claim 8 or claim 11, or chosen from the sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10, or a cell as claimed in claim 24 or a non-human transgenic organism as claimed in claim 25, and a second step consisting in detecting the complex formed between the candidate chemical or biochemical compound and the protein or the cell or the transgenic organism.

     36. A medicinal product comprising a product chosen from the polynucleotides as claimed in any one of claims 8, 11 or 12, the proteins or protein fragments encoded by a polynucleotide as claimed in claim 8 or claim 11, the polypeptides of sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10, the antibodies specific for the protein of SEQ ID NO. 2, the vectors as claimed in claim 23 and the modified cells as claimed in claim 24.

     37. The use of a product chosen from: the polynucleotides as claimed in any one of claims 8, 11 or 12, the proteins or protein fragments encoded by a polynucleotide as claimed in claim 8 or claim 11, the polypeptides of sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10, the antibodies specific for the protein of SEQ ID NO. 2, the vectors as claimed in claim 23 and the modified cells as claimed in claim 24, for preparing a medicinal product intended for the prevention and/or the treatment of diabetes, particularly that associated with the presence of at least one mutation of the gene corresponding to SEQ ID NO. 1, and/or with abnormal expression of the protein

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corresponding to SEQ ID NO. 2, or intended for the prevention and/or the treatment of hyperinsulinisms when abnormal expression, maturation or secretion with respect to the insulin gene is observed, or intended to

5   regulate the maturation and/or secretion of insulin in the beta cells or in cells that are to be modified for the purpose of insulin secretion, or intended to regulate beta cell apoptosis phenomena.

          38.  The use of a product chosen from: the

10  polynucleotides as claimed in any one of claims 8, 11 and 12, the proteins or protein fragments encoded by a polynucleotide as claimed in claim 8 or claim 11, the polypeptides of sequences SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9 and SEQ ID NO. 10 and the antibodies

15  specific for the protein of SEQ ID NO. 2, for determining an allelic variability, a mutation, a deletion, a loss of heterozygocity or any anomaly of the gene encoding said protein.